

Prudden (J. M.)

STUDIES



ON THE

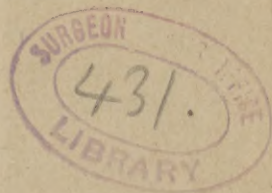
ETIOLOGY OF DIPHTHERIA

SECOND SERIES

BY

T. MITCHELL PRUDDEN, M.D.

DIRECTOR OF THE LABORATORY OF THE ALUMNI ASSOCIATION, COLLEGE OF
PHYSICIANS AND SURGEONS, NEW YORK



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IN an experimental study on the etiology of diphtheria, published by the writer in 1889,¹ a brief summary was given of the more important bacteriological studies which had been made of this disease, up to that time, by the new methods in various countries. This summary showed that the attention of the observers had been largely centred on two species of bacteria, which, sometimes apart, sometimes together, had been so frequently found in the pseudo-membranes as to give rise to a justifiable belief that one or other or both of them might be the cause of the disease. These bacteria were the so-called *Bacillus diphtheriæ* of Loeffler, and a streptococcus which most observers are inclined to believe identical with the *Streptococcus pyogenes* and *Streptococcus erysipelatos*. The evidence which had accumulated along these lines was largely such as was derived from the presence of these germs in the local lesion or elsewhere in the bodies of the victims of diphtheria. The results of animal experiments were in so far indecisive as that, while they showed that both forms of bacteria were in different ways pathogenic, neither of them was capable of inducing a disease which could be fairly considered absolutely identical with human diphtheria. The animal experiments with the *Bacillus diphtheriæ* were by far the most convincing in this regard, inasmuch as with this germ a pellicle somewhat analogous to the pseudo-membrane of diphtheria could be produced by their application to a wounded mucous membrane, and in some animals, notably the guinea-pig, death regularly followed subcutaneous injections of cultures, with definite and fairly constant lesions. The lack of precision in our conception of what should be called, strictly speaking, diphtheria, and what forms of disease associated with the development of a pseudo-membrane, if any, should be held apart from it, has led

¹ Prudden: *The American Journal of the Medical Sciences*, May, 1889

to much uncertainty as to the interpretation of the results of all these studies. Clinical observers in this country have been disposed of late—erring, if erring at all, on the side of safety—to consider and to treat all pseudo-membranous inflammations as if they were the local expression of the acute infectious disease which has been called diphtheria.

This condition of affairs, however, wise as its perpetuation might seem to be from the practical standpoint of the bedside adviser, is most confusing and unfortunate from the point of view of the seeker after the primary causes of all these phases of pseudo-membrane inflammation, because it is fully established that a pseudo-membranous inflammation of the mucous membranes may be induced by a variety of agents.

As the result of a summary made in the paper above alluded to, in 1889, of the cases from which the bacillus of Loeffler had been isolated by culture, and its virulence proved by animal inoculations, it was found that this bacillus had been cultivated from 24 out of 28 cases, thus far fully studied.¹ Fuller reports of studies not included in the above summary on account of too meagre details then at hand, and studies made since that time, which have been numerous and important, show the following results so far as the bacillus of Loeffler is concerned :

Babes² found the *Bacillus diphtheriæ* in all of 42 cases of diphtheria ; D'Espine³ found it in 14 cases ; Ortmann⁴ in 15 out of 16 cases ; Spronk, Wintgens and Van den Brink⁵ in all of 7 cases ; Roux and Yersin⁶ in all of 15 cases ; Kolisko and Paltauf⁷ in 50 cases ; Zarniko⁸ in 18 out of 20 cases ; Beck⁹ in 50 out of 52 cases ; Sørensen¹⁰ in 7 out of 10 cases ; Escherich¹¹ in 20 out of 22 cases ; Tangl¹² in all of 18 cases ; Brieger and Fraenkel¹³ in all of 22 cases.

We have thus on record at the present time, so far as the literature is available to the writer, the results of the

¹ See supplementary note at the end of this paper referring to studies just published by Welch & Abbott.

² Babes : *Zeitschrift für Hygiene*, Bd. 5, p. 177.

³ D'Espine : *Revue médicale de la Suisse romande*, 1888, No. 1, p. 49.

⁴ Ortmann : *Berliner Klin. Wochenschrift*, 1889, No. 10, p. 218.

⁵ Spronk : Wintgens and Van den Brink, *Nederl. Tydschrift, v. Geneeskunde*, 1889, Ded. II., Nos. 22 and 23. *Centralblatt für Allg. Path. und Path. Anat.*, Bd. 1, p. 218, 1890.

⁶ Roux and Yersin : *Annales de l'Institut Pasteur*, 1888, No. 12.

⁷ Kolisko and Paltauf : *Wiener Klin. Wochenschrift*, 1889, No. 6.

⁸ Zarniko : *Inaug. Dissertation*, Kiel, 1889.

⁹ Beck : *Zeitschrift für Hygiene*, Bd. 8, p. 434.

¹⁰ Sørensen : *Nordiskt medicinskt. Arkiv.*, 1886, Bd. 18, No. 25.

¹¹ Escherich : *Centralblatt für Bakteriologie*, January 2, 1890, p. 8.

¹² Tangl : *Centralblatt für Allg. Path. und Path. Anat.*, Bd. 1, p. 795, 1890.

¹³ Brieger und Fraenkel : *Berliner Klin. Wochenschrift*, March 17, 1890, p. 242.

examination of 316 cases of so-called diphtheria, in 302 of which the bacillus of Loeffler was found.

A large number of control examinations by various observers have established the fact that this virulent bacillus is rarely, if ever, found in the body except in the local lesion of diphtheria, and is almost never present in any other disease or in health. A so-called pseudo-diphtheria bacillus has been found both in the membrane of diphtheria and in healthy or otherwise diseased individuals. This bacillus is morphologically, as well as biologically, similar to, if not identical with, the *Bacillus diphtheriæ*, but is not virulent on inoculation into guinea-pigs or the commonly employed animals.

Very significant experiments on animals with a poison developed in the cultures of the Loeffler bacillus, a poison capable of inducing delayed paralyses and other toxic symptoms,¹ as well as various other collateral studies which cannot be considered here, serve to reinforce the evidence now at hand, that the *Bacillus diphtheriæ* of Loeffler is the causative agent, in a large proportion of cases at least, of the disease commonly spoken of as diphtheria.

On the other hand, a large proportion of the observers who have found the Loeffler bacillus in the pseudo-membranes of diphtheria, have found more or less frequently associated with it a streptococcus apparently identical with the *Streptococcus pyogenes* and *Streptococcus erysipelatos*. Furthermore, there is recorded a considerable number of cases of pseudo-membranous inflammation closely simulating, if not identical morphologically and clinically, with diphtheria, in which not only is the *Bacillus diphtheriæ* of Loeffler absent, but in which the above-mentioned streptococcus is nearly constantly present. These forms of so-called diphtheria are most commonly associated with scarlatina and measles, erysipelas and phlegmonous inflammation, or occur in individuals exposed to these diseases; but whether exclusively under these conditions, is not yet fully established.

Thus Loeffler² says as the result of his work: "That the chain-forming micrococcus can cause a disease similar to diphtheria when it enters the pharynx and spreads toward the lungs in the tracheal lymph-channels, I consider very probable." Fraenkel³ found a streptococcus in nearly pure culture in two cases of somewhat atypical diphtheria; Raskin⁴ found a streptococcus, but not

¹ Roux and Versin: *Annales de l'Inst. Pasteur*. Spronk: *Centralblatt für Allg. Path. & Path. Anat.* Bd. 1, p. 221.

² Loeffler: *Mitth. a. d. Kais. Gesundheitsamte*, Bd. 2, 1884.

³ Fraenkel: *Zeits. für Klin. Med.*, Bd. 13, H. 1, S. 19, N 26.

⁴ Raskin: *Centralblatt für Bakteriologie*, Bd. 5, 13 and 14.

the Loeffler bacillus, in two out of three cases of so-called scarlatinal diphtheria. In a series of cases of scarlatinal diphtheria studied by Heubner¹ the bacillus of Loeffler was wholly absent, but a streptococcus was always present. Wurz and Bourges² found in nine cases of scarlatina, in which the diphtheritic lesion developed early, that the bacillus of Loeffler was absent, while a streptococcus similar, but, according to them, not absolutely identical with the *Streptococcus pyogenes*, was present in all. In two cases in which the diphtheritic lesion developed late, the bacillus of Loeffler was found. Roux and Yersin,³ in three cases supposed clinically to be diphtheritic from the development of a pseudo-membrance on and behind the tonsil, and in one case on the tongue and lips, failed to find the *Bacillus diphtheriæ* (Loeffler), but did find cocci, in two of the cases of well-marked streptococcus form.

Chantemesse and Widal have reported cases in which a fibrinous exudate similar to that of diphtheria was associated with a streptococcus.

In the series of studies of 24 cases by the writer in 1889, already alluded to, the bacillus of Loeffler was absent in all, but a streptococcus apparently identical with the *Streptococcus pyogenes* was found in 22. This result, negative, so far as Loeffler's bacillus is concerned, has seemed to excite dissatisfaction among many of the German reviewers of the article, since it has been interpreted by them as speaking against the etiological importance of Loeffler's bacillus, an interpretation which was not drawn by the writer in the article in question, and which seems to him wholly unjustifiable.

In view of the doubt existing among practitioners as to whether all forms of pseudo-membranous inflammation should be called diphtheria, or not, and with the purpose of making a wholly objective study, the writer distinctly stated at the outset of that paper, that all the fatal cases of extensive pseudo-membranous laryngitis, as well as pharyngitis, should in his study be considered as cases of diphtheria. This left the question as to the propriety of establishing separate groups of pseudo-membranous inflammation open and free from bias. It was distinctly stated, however, that 16 out of the 24 cases occurred in a large asylum, in which measles and scarlatina were prevalent during the period in which these studies were under way. Five other cases from another asylum were exposed to similar conditions. Furthermore, it is set forth in the

¹ Huebner: *Jahrb. für Kinderheilkunde*, Bd. 31, 1890, p. 56.

² Wurz and Bourges: *Arch. de Méd. Exp.*, May 1, 1890.

³ Roux and Yersin: *Annales de l'Institut Pasteur*, July, 1890, p.

clinical histories of the individual cases, that 2 were associated with whooping-cough, 2 with umbilical phlegmon, 1 with chicken-pox, 2 with scarlatina, 1 with rectal abscess, 1 with erysipelas of the vulva, 4 with measles. While no such complications existed in the individual, in the remaining ten cases, the fact that they were largely (all but two) children intimately associated with those exhibiting one or other of the complicating disorders, was not perhaps sufficiently emphasized, but seemed to the writer so patent from his preliminary statements, that it was not deemed necessary to call specific attention to it.

We should not forget that there is a very significant possibility that sensitive children closely associated in nursery wards with others suffering from scarlatina, measles, and erysipelas may, though not actually affected with these diseases themselves, still be liable to acquire those complicating forms of disease which find expression in a pseudo-membranous pharyngitis and laryngitis.

In the conclusions which were drawn from the results of these examinations, the writer stated that, "It should be distinctly understood that these studies on the etiology of diphtheria, and the conclusions derived from them, apply only to a certain set of cases. It by no means follows that because this particular group of cases of diphtheria is caused by a streptococcus, and seems to be intimately related in etiology to some other common phase of inflammation, that all cases of diphtheria are induced by the same organism, or are related in the same way to erysipelas and phlegmon."

That other organisms than the streptococcus here described may induce that set of symptoms and lesions to which we give the name diphtheria, we must, of course, admit, and this the more readily on account of the great variability of both symptoms and lesions in even well-marked groups of cases. So far as Loeffler's experiments go, they tend to indicate that some other forms of bacteria really may play a part in the induction of certain forms of the disease." And further, "On the whole, it seems to me that, considering the insusceptibility of animals to diphtheria as we know it in man, the result of all these series of experiments taken together, abundantly justifies us in the assumption that in a certain class of cases, at least, diphtheria is caused by a streptococcus having the character set forth above."

In view of the apparent discrepancy between the results taken as a whole, and those of other observers, the writer has been over the material which served as the basis of these researches, so far as it was still available, and fails to find any reason for a revision of his results or his conclusions.

Of course, one would not for a moment deny the possibility of the Loeffler bacillus having been overlooked in some of these cases, since the experimental error is not inconsiderable in all studies of this kind. Here a negative result is, however, never of equal weight with a positive one. But the extremest care was used, and I do not think there was any oversight. It is furthermore not beyond the bounds of possibility, as Baumgarten¹ suggests, that the Loeffler bacillus may lose its vitality early in the presence of large numbers of other bacteria, such as the streptococci, and so may not be revealed in the cultures.

It has been suggested, and upon this point much stress has been laid, that the culture medium largely employed by the writer for the plate cultures, namely, glycerine-agar, is not as favorable for the purpose as is the blood-serum mixture employed and recommended by Loeffler, since on it, the growth of the Loeffler bacillus is not so rapid in comparison with that of other bacteria. That it is sufficiently well adapted to this purpose, to say the least, is shown by its recommendation and employment by several reliable observers, and by the fact that the writer has found no difficulty in separating by its use the Loeffler bacillus in cases of diphtheria in which that germ was present, as it was in most of the new series of cases presently to be described. Glycerine-agar (six per cent. glycerine) is a perfectly good and wholly reliable medium for the cultivation of the *Bacillus diphtheriæ* of Loeffler, and for its separation from other forms of bacteria which may be present in the various forms of pseudo-membrane. But to be successful with this medium, it is wise, as was always done in the experiments in question, to make numerous plates, and to make the streaks upon the agar on these plates so dilute and so numerous that the Loeffler bacillus will have the opportunity when present to grow sufficiently for recognition and resowing in some places at least without overgrowth by, or interference with, other forms of germs.

The whole, or at least the main, difficulty in this matter seems to the writer to be one not of technique, not of imperfect observation, but one first of nomenclature, and second of premature assumption as to the unity of cause in pseudo-membranous inflammations. In other words, in order to decide positively what causes diphtheria, we need to know positively what symptoms or lesions shall be recognized as characterizing it, in distinction from other allied symptoms and lesions, if such exist, which are of different nature and different origin. If we cannot determine this at the bedside, we must strive by the

¹ Baumgarten : Jahresbericht über die Fortschritte in der Lehre von den pathogenen Mikroorganismen, 1889, p. 215.

new biological methods to gain such knowledge of the etiology of the whole group as shall enable us to decide whether or not it should be divided into separate classes.

In view of the condition of affairs at present existing, and as it did not seem at all probable that the disease properly called diphtheria could have a specific bacterial cause different in America from that known in Europe, it has seemed incumbent on the writer to undertake a new series of studies on a set of cases from which the complicating conditions existing in most of the previous cases should be so far as possible eliminated.

The cases now to be recorded, twelve in number,¹ were cases of fatal pseudo-membranous inflammation occurring in two children's asylums, in which for many months there had been no scarlatina and no measles, and in which there were no complicating suppurative inflammations and no erysipelas. In one case only was there the complication of whooping-cough.

The following are the cases and the results of their examination :

CASE I. *Clinical History.*—Female, three and one-half years of age. September 22, 1890, pharyngeal pseudo-membrane. September 24th, laryngeal symptoms. September 25th, 5 A.M., intubation, followed by rise of temperature, 108° F.; died at 12 P.M., cyanotic.

Autopsy.—A dense, firm, closely adherent membrane on both tonsils, on posterior surface of epiglottis, and extending throughout larynx and trachea down to medium bronchi; loosened and thinner below. Lungs: deep congestion with broncho-pneumonia in both posterior lobes. Kidneys: parenchymatous degeneration.

Bacterial Examination, Morphological.—Moderate numbers of stout bacilli in older parts of pseudo-membrane, with considerable numbers of cocci in masses and scattered.

Cultures.—Membrane, the most abundant colonies showed the characteristic mode of growth of the *Bacillus diphtheriæ* (Loeffler) on the plates and in tube-cultures of glycerine-agar, gelatin, and beef-tea; stained specimens from these cultures showed the characteristic bizarre form. I do not give a detailed description of the morphology and biology of these bacilli, since no new observations were made on them and they corresponded in all respects

¹ A large part of the material used in this study came from the New York Infant Asylum, Mount Vernon, N. Y., from the service of Dr. Robert Millbank. For this material and for his most valuable collaboration in other ways, I wish to express my indebtedness to Dr. Charles G. Kerley, Resident Physician of the New York Infant Asylum. The remainder came from the New York Foundling Asylum, and for this I am indebted to Dr. Wm. P. Northrup and Dr. G. S. Lynde.

with the well known and definite descriptions so often reported. Almost equally abundant were colonies, cultures from which gave the characters of *Streptococcus pyogenes*. There were also numerous colonies of *Staphylococcus pyogenes aureus*, and a few scattering forms, mostly bacilli. Cultures from the kidneys were negative.

Animal Experiments.—Inoculation of the sediment of beef-tea cultures four days old of the bacillus resembling the bacillus of Loeffler into a guinea-pig, was followed by death within thirty-six hours, with hemorrhagic œdema, and a localized whitish exudate at the seat of injection; effusion into the serous cavities, and a moderately swollen spleen. Cultivations from these animals gave pure cultures of Loeffler's bacillus from the exudate at the seat of inoculation, and no growth whatsoever from the heart's blood and viscera.

Remarks.—This child was quarantined with several other children before it became ill, and developed its disease at the same time as another child, and there were three more cases in the same building immediately following these.

CASE II. *Clinical History.*—Female, aged three years and ten months. January 5, 1891, membrane seen on pharynx and continued there, with an unusual amount of white membrane forming in pharynx and nose. January 16th, intubated, and much membrane coughed up. January 21st, suddenly grew much worse, with heart failure; rallied twice, but dropped dead at 6 P.M.

Autopsy.—Loosening membrane from tip of epiglottis down into medium bronchi. Lungs: broncho-pneumonia in middle and upper lobe posteriorly. Kidneys: parenchymatous degeneration.

Bacterial Examination, Morphological.—Large numbers of cocci massed and scattered in pseudo-membrane; no bacilli found.

Cultures.—Membrane, large numbers of colonies of streptococcus having the characters of *Streptococcus pyogenes* developed on the plates from the pseudo-membrane; also considerable numbers of *Staphylococcus pyogenes aureus*. The bacillus of Loeffler did not develop on any of the plates. Cultures from the lungs and from the kidneys showed considerable numbers of *Streptococcus pyogenes* and *Staphylococcus pyogenes aureus* and nothing else.

Remarks.—This case had not, so far as known, been exposed to diphtheria, and there were no cases in the nursery for three months previously.

CASE III.—Male, aged two years and ten months. February 1, 1891, croupy in the evening; membrane over pharynx. February 2d, severe dyspnoea; intubation.

February 3d, albumin in urine; temperature, 104° F.; cyanotic; no evidence of pneumonia. February 4th, died.

Autopsy.—Dense membrane on tonsils and in larynx and trachea down to first bronchi. No pneumonia; parenchymatous degeneration of kidneys.

Bacterial Examination, Morphological.—Large numbers of bacilli, single and clustered in the more superficial part of the pseudo-membrane; also large masses of cocci, single and in chains.

Cultures.—Membrane, moderate numbers of colonies resembling on the plates and in subsequent tube cultures, the *Bacillus diphtheriæ* (Loeffler), enormous numbers of colonies of *Streptococcus pyogenes*, considerable numbers of colonies of *Staphylococcus pyogenes aureus*. Lung cultures contained a few colonies of Loeffler's bacillus, many streptococci, and a few staphylococci. Kidney cultures were negative.

Animal Experiments.—A guinea-pig inoculated subcutaneously with the sediment of a four-days old beef-tea culture of the Loeffler's bacillus, died thirty-six hours after, with the usual local lesions, cultures from which showed the specific bacillus, while visceral and blood cultures were negative.

Remarks.—There had been no diphtheria in the nursery for at least two months before this child was attacked.

CASE IV.—Female, aged two years and eight months. Had whooping-cough and a broncho-pneumonia early in January, 1891, which ran a short course; was exposed to diphtheria late in January. February 1st, croupy; temperature 102° F., with loose patches of exudate on tonsils; might from appearance have been called follicular tonsillitis. February 2d, temperature, 102° F. to 104° F.; intubation. February 7th, evidence of lung consolidation left posterior. February 8th, tube removed; continued growing worse. February 11th, died. The whooping cough continued throughout the course of the diphtheria.

Autopsy.—Moderate membrane, loosened and disintegrating and peeling off below from epiglottis to larger bronchi. Moderate amount of broncho-pneumonia and congestion in posterior lobes of lungs.

Bacterial Examination, Morphological.—Found no bacilli in the loose shreds of membrane still adhering to surface, but these, as well as the superficial layer of the mucosa, showed many cocci single and in masses.

Cultures.—From the membrane there developed on the plates very large numbers of characteristic colonies of the *Bacillus diphtheriæ* (Loeffler), characteristic also in tube cultures. Also large number of colonies of

Streptococcus pyogenes and a moderate number of *Staphylococcus pyogenes aureus*. From the lungs grew on the plates many streptococci and a few staphylococci.

Animal Experiments.—A guinea-pig inoculated subcutaneously with the sediment of a five days old beef-tea culture of the Loeffler bacillus, died on the second day with the characteristic lesions, and gave positive cultures from seat of inoculation, negative from blood and viscera.

CASE V.—Female, aged twenty-one days; good condition at birth. February 17th, sick. February 18th, cyanotic with extreme laryngeal obstruction. No membrane visible; epiglottis not swollen; temperature $102\frac{1}{2}^{\circ}$ F. Intubation; large piece of membrane coughed up, with considerable relief. February 19th, cyanotic; collapse; death.

Autopsy.—Pharynx normal; no distinct membrane in air-passages, but a turbid adhesive exudate in larynx and trachea. Broncho pneumonia posteriorly, with congestion and punctate hemorrhages. Kidneys, spleen, and liver appear normal.

Bacterial Examination, Morphological.—No bacilli found; moderate numbers of cocci, single and clustered and in chains, penetrating the mucosa in the larynx.

Cultures.—From the scrapings of trachea and larger bronchi there developed on the plates a few colonies characteristic of the *Bacillus diphtheriae* (Loeffler); very many of *Streptococcus pyogenes* and many of *Staphylococcus pyogenes aureus*. The lung contained, as shown by cultures, enormous numbers of *Streptococcus pyogenes*, and a few of *Staphylococcus pyogenes aureus*. On the kidney plates developed many streptococcus colonies. From the spleen and liver nothing grew.

Animal Experiments.—Large guinea-pig inoculated subcutaneously with sediment of beef tea culture of the Loeffler bacillus died in thirty-six to forty eight hours, showing characteristic lesions, with the specific germs only at the seat of inoculation.

CASE VI.—Male; aged one month, eight days. On February 19th, came into hospital with bad naso-pharyngeal diphtheria. Membrane reformed with great rapidity if removed. Broncho-pneumonia developed. Death, February 22d.

Autopsy.—Dense, tough, closely adherent patches of pseudo-membrane in the pharynx and about base of epiglottis, a small amount in the upper part of the larynx; none below. Lungs, dense; broncho-pneumonia posteriorly. Kidneys: marked parenchymatous degeneration. Liver, congested. Spleen soft and slightly enlarged.

Bacterial Examination, Morphological.—Large numbers of bacilli in masses in the superficial parts of the

pseudo-membrane ; also numerous cocci, but slightly penetrating.

Cultures.—From the pseudo-membrane in pharynx developed an enormous number of colonies characteristic of the *Bacillus diphtheriæ* (Loeffler) ; large numbers of *Streptococcus pyogenes*, and many of *Staphylococcus pyogenes aureus*.

Lung plates showed a nearly pure culture of enormous numbers of streptococci and a few of the staphylococcus. From the liver and spleen developed considerable numbers of streptococci and nothing else, while the kidney cultures were negative.

Animal Experiments.—A large guinea-pig inoculated with sediment of a four days old beef-tea culture died on the eighth day, showing the typical local lesion, with the Loeffler bacillus present at seat of inoculation, and nowhere else. A second animal, inoculated with a three days old culture, died on the second day with typical local lesion.

CASE VII.—Male, aged twenty-three months. January 9th, tonsils swollen and congested ; pharynx and fauces congested. January 10th, croupy, with laryngeal obstruction ; hoarseness ; dyspnoea ; prostration and increasing cyanosis ; râles over chest ; temperature, 102° to 104° F. ; no exudation visible ; intubation, which gave marked relief. January 11th, respiration frequent ; congestion and swelling of tonsils continues, but no exudate visible ; prostration. Failed and died 5.15 P.M.

Autopsy.—Moderately dense and voluminous membrane from tip of epiglottis down to bifurcation of trachea, and extending on right side to finer bronchi, on the left into first divisions. Broncho-pneumonia in both lower lobes, and middle right vesicular emphysema.

Bacterial Examination, Morphological.—Small numbers, clustered and scattered, of short, rather stout bacilli, and few cocci in pseudo-membrane.

Cultures.—Large numbers of colonies on plate with characteristics here and in subsequent tube cultures of the *Bacillus diphtheriæ* (Loeffler), considerable numbers of *Streptococcus pyogenes*, and a few *Staphylococcus pyogenes aureus*.

Animal Experiments.—Large guinea-pig inoculated subcutaneously with sediment of five days old beef-tea culture of the Loeffler bacillus, died on third day with characteristic lesions, cultures showing the specific bacillus at seat of injection, but nowhere else.

CASE VIII.—Female, aged fifteen and one-half months. January 12th, cervical lymph-nodes and tonsils swollen ; fauces and pharynx congested ; temperature, 100° F. January 13th, breathing labored ; prostration ;

intubation; temperature, 104° F. January 14th, thick granular exudate scattered over tonsils and palate; breathing labored; temperature, 105° F. January 15th, temperature, $104\frac{1}{2}^{\circ}$ F.; died at 3 P.M., after two convulsive seizures.

Autopsy.—From tip of epiglottis to middle of trachea, shreds of membrane loosely adherent. Dense membrane from middle of trachea down into finer ramifications of bronchi. Broncho-pneumonia in posterior part of both lower lobes; vesicular emphysema. Kidneys showed parenchymatous degeneration, as did liver. Spleen slightly enlarged and soft.

Bacterial Examination, Morphological.—Moderate numbers of stout, short bacilli in pseudo-membrane.

Cultures.—Large numbers of colonies of *Bacillus diphtheriae* (Loeffler). A small number of *Staphylococcus pyogenes*, and a considerable number of a slender short bacillus (not identified).

Animal Experiments.—A large guinea-pig injected subcutaneously with sediment of a three days old beef-tea culture of the Loeffler bacillus, died on the third day with characteristic lesions, and localization of the germs to seat of injection.

CASE IX.—Female, aged eleven and one-half months. January 7th, spot on left tonsil size of flaxseed; temperature, 103° F. January 8th, thick, yellow, cheesy exudate on both tonsils, size of split pea; restless; cough; temperature, $104\frac{1}{2}^{\circ}$ F. After this the tonsils cleared, and the temperature went down to 99° F., 100° F., then the exudate reappeared; child was hoarse and croupy with pulmonary obstruction, with temperature $104\frac{1}{2}^{\circ}$ F. on January 16th and 17th; prostration and cyanosis supervened; pharyngeal exudate increased; pneumonia developed; temperature between 103° F. and 104° F., with death on January 20th.

Autopsy.—Membrane extending from tip of epiglottis to smaller bronchi; pneumonia of both lungs.

Bacterial Examination.—This was made from a fragment of membrane coughed up on January 19th. Cultures from this showed large numbers of the *Bacillus diphtheriae* (Loeffler) and a considerable number of the *Streptococcus pyogenes*.

Animal Experiments.—Inoculations of two large guinea-pigs caused death in both, with characteristic lesions.

CASE X.—Female, aged seven and one-half months. January 25th, throat congested; temperature, 102° F. January 26th, large membrane on right tonsil; temperature, $102\frac{1}{2}^{\circ}$ F. January 27th, exudate on both tonsils and between uvula and right pillar; temperature, $104\frac{1}{2}^{\circ}$ F. January 28th, croupy; some pulmonary obstruction;

râles over chest; temperature, $104\frac{1}{2}^{\circ}$ F.; prostration came on; exudation in nose and lip and over fauces; cyanosis; temperature between 104° and 105° F.; dyspnoea. Death, February 5th.

Autopsy.—Softening, dark-colored membrane in larynx and trachea, extending into smaller bronchi. Moderate broncho-pneumonia in both posterior lower lobes, with general vesicular emphysema. Kidneys congested, with parenchymatous degeneration. Liver congested. Spleen firm.

Bacterial Examination, Morphological.—The pseudo-membrane was crowded in places with masses of cocci penetrating deeply into the underlying tissues. Here and there, but in no part very abundantly to be seen, were bacilli having the form and size of the *Bacillus diphtheriæ*, either in clusters by themselves or scattered among the cocci.

Cultures.—From the membrane grew on the plates large numbers of colonies of the *Bacillus diphtheriæ* (Loeffler). Enormous numbers of *Streptococcus pyogenes* and many of *Staphylococcus pyogenes aureus*. From kidneys, spleen, and liver were cultivated *Streptococcus pyogenes* in considerable numbers, and nothing else.

CASE XI.—Female, aged ten and one-half months. February 13th, throat congested, with minute exudate on both tonsils; temperature, 102 to 105.2° F. February 14th, A.M., posterior surface of uvula covered with membrane; serous discharge from nose; temperature, 101.8° F. to 103.6° F. P.M.; membrane covers both tonsils and spaces between pillars and uvula. February 15th, croupy; increasing obstruction; albumin sixty per cent. by vol. Died.

Autopsy.—Voluminous membrane in pharynx and over epiglottis, extending down to the lower bronchi; no pneumonia, but moderate congestion of posterior portions of lungs. Kidney, parenchymatous degeneration; spleen enlarged and soft; liver normal.

Bacterial Examination, Morphological.—Large numbers of intermingled short bacilli and cocci in pseudo-membrane and penetrating underlying tissues.

Cultures.—From the membrane there developed on the plates small numbers of colonies, proving on subsequent tube cultures to be the *Bacillus diphtheriæ* (Loeffler), but their growth was meagre. Enormous numbers of *Streptococcus pyogenes* developed, and many of *Staphylococcus pyogenes aureus*. Cultures from kidneys, liver, and spleen were negative; those from the lungs showed a very few colonies of the *Staphylococcus pyogenes aureus*.

Animal Experiments.—Guinea-pig died on second day with characteristic lesions.

CASE XII.—Female, aged nine months. February

18th, throat severely congested; hoarse; temperature, 102° F. February 19th, minute dots on both tonsils; croupy; laryngeal obstruction; increasing temperature, 104° F.; intubation. February 20th, exudation on both tonsils, extreme prostration; temperature, 105° F. February 21st, membrane covering both tonsils and uvula; breathing labored; dulness over both lower lobes; temperature, 104° F. February 22d, death.

Autopsy.—The larynx was covered with a thin, closely adherent pellicle, extending throughout the trachea and into the second branches of the bronchi. Broncho-pneumonia in posterior portions of both lungs. Kidneys show marked parenchymatous degeneration, as does also the liver; spleen large and soft.

Bacterial Examination, Morphological.—Large numbers of cocci, single and in large clusters, in the superficial and deep layers of pseudo-membrane. No bacilli could be found.

Cultures.—From the membrane were cultivated the *Bacillus diphtheriae* (Loeffler) in moderate numbers; large numbers of *Streptococcus pyogenes* and many colonies of *Staphylococcus pyogenes aureus*, *albus*, and *citreus*. The lung cultures showed many streptococci, and a very few staphylococci and Loeffler's bacillus. On the spleen and liver cultures a few colonies of streptococcus grew. The kidney cultures were negative.

Animal Experiments.—Inoculation of medium-sized guinea-pig with sediment of four days old beef-tea culture of the Loeffler bacillus caused death on second day, with characteristic lesions and growth of the specific germ from the seat of injection; no growth from the blood or viscera.

We have thus, in this series of twelve wholly uncomplicated cases of diphtheria, found the *Bacillus diphtheriae* (Loeffler) in eleven, and, as is usual, only at the seat of local lesion. A streptococcus having the characters of *Streptococcus pyogenes* was also present in the pseudo-membrane in eleven of the cases; in the kidney in three; in the liver and spleen in three. The *Staphylococcus pyogenes aureus* was present in the membranes in eleven of the cases; in the kidneys in one; in the liver and spleen in one. No other bacteria were present with any uniformity or marked abundance in any of the cases.

My own observations are quite in accord with those of Loeffler in regard to the occasional occurrence in both the healthy and diseased pharynx of streptococci, which are in many respects different from the *Streptococcus pyogenes*. These occasional forms have not been considered in this study, nor the scattering species of other kinds, since they do not seem to come within the scope of the subject in hand.

Nor have I given here the details of technique, since it was in all respects similar to that employed and sufficiently fully described in my former paper.

More and more clearly it appears, as such studies accumulate, that there is one large and important class of cases of pseudo membranous inflammations constantly associated with a particular species of micro organism, the *Bacillus diphtheriæ* of Loeffler, which stands in a causative relation to the disease. That a streptococcus often plays a very important, though most likely a secondary, rôle in these cases, seems certain. Equally certain is it in the writer's belief that other classes of cases, often grouped with these and often lacking distinguishing clinical features, are caused by a streptococcus closely similar to, if not identical with, *Streptococcus pyogenes*, and called the *Streptococcus diphtheriæ*.

Sufficient evidence has now at last accumulated along the lines of work indicated, so that we are justified, in the writer's opinion, in giving that precision to the problems grouped about the cause, prevention, and treatment of pseudo-membranous inflammations, which has so long been wanting.

We are now, it would seem, justified, as it did not appear to the writer that we were two years ago, owing to the large number of important researches which have been made in the interim, in saying that the name diphtheria, or at least primary diphtheria, should be applied, and exclusively applied, to that acute infectious disease, usually associated with a pseudo-membranous inflammation of the mucous membranes, which is primarily caused by the bacillus called *Bacillus diphtheriæ* of Loeffler. That this disease is often modified in its course and manifestations by the presence at the seat of local lesion and elsewhere of other pathogenic bacteria, must be assumed as probable. That other forms of acute infectious diseases exist associated with a pseudo-membranous inflammation of the mucous membranes, and caused by wholly different germs, is, as it seems to me, also fully established.

But if the name diphtheria can be universally and exclusively applied to the disease caused by the bacillus of Loeffler, and the latter be regarded as the test of diagnosis, we shall be in a condition to work with definiteness at the various accessory problems, and study more clearly diseases which cluster about and complicate, and not infrequently simulate, the more common and important and fatal disease.

What this class of diseases not caused by or associated with the Loeffler bacillus should be called in distinction from diphtheria, it will perhaps not be possible to say until more extended researches shall have been made upon

them, and the specific conditions under which they occur are more definitely known.

It should be clearly held in mind by those eager to draw from experimental studies on the etiology of this disease such practical lessons as shall be of value in treatment, that whether one or more causative agents are at work in setting up those acute infectious diseases which are associated with the formation of a pseudo-membrane, it seems to be fully established that in all of the cases the seat of infection and the origin of the mischief is always a local one. All these experiments point to the paramount importance of efficient local germicidal treatment, and this is equally important whether the bacillus of Loeffler, or the streptococcus, or both together be the infecting agent.

It is the complicating broncho-pneumonia and the systemic poisoning which carry off a large proportion of the victims of pseudo-membranous pharyngitis and laryngitis. That the pneumonia is largely dependent, in many cases, at least, upon the streptococcus, which is so frequently present, seems pretty well established. How much of the systemic affection is due to the streptococcus when this is present in the membrane and in the viscera, as is so often the case, and how much to a poisonous material absorbed from the seat of growth and development of the Loeffler bacillus in the local lesion, it is not possible at present definitely to say. That the poison locally produced by the Loeffler bacillus can and usually does alone cause the characteristic systemic effects in primary diphtheria, is well established.

It seems to the writer that a simple "Liquet" may be uttered on this subject, not as Loeffler¹ believes when such experimental results as seem at the first sight to be out of harmony with his conclusions "shall have been shown to be incorrect," but when they shall be judged on the basis of a definite nomenclature and apart from the thrall of a too limited conception of the nature of those acute infectious diseases which have not a wholly definite characteristic and constant local lesion.

NOTE.—A new and most interesting and important study of eight cases of diphtheria by Welch and Abbott² of the Johns Hopkins University, which I regret not to be able to consider in detail has been published since this article was sent to the RECORD. These observers found in all of their cases the *Bacillus diphtheriæ* of Loeffler. All of their cases were from private practice, and their studies

¹ Loeffler: *Deutsche Med. Wochenschrift*, February 6, 1890, p. 111.

² Welch and Abbott: *Bulletin of the Johns Hopkins Hospital*, vol. ii., No. 11, 1891.

were made from bits of membrane removed during life. Welch and Abbott have determined, contrary to the observation of most of the continental experimenters, that the *Bacillus diphtheriæ* grows on potato. Their article contains an interesting summary of the later studies on the systemic effects of the poison developed in the growth of this germ, and the conference of immunity by the method of Fraenkel and Behring, to which I can only refer. I am pleased to notice that the critical estimate of Welch and Abbott of my earlier studies, leads them to regard the difference of result obtained from that of most of the continental observers, as due to the peculiar nature of the cases which, as I have indicated in this article, seem to be not primary diphtheria but dependent upon the complicating conditions under which the cases occurred.

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